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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	7

DATE MAILED: 05/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/466,935	LIVSHITS ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE f this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-10 is/are pending in the application.

4a) Of the above claim(s) 5-7 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4 and 8-10 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims 1-10 are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-10 are pending in the application.

It is noted that reference AV was not included in the Information Disclosure Statement submitted in Paper No. 2, filed 03/31/00. In order for reference AV to be considered by the Examiner, a copy of this reference should be provided. Upon receipt and consideration of reference AV, Form PTO-1449 filed in the above mentioned Paper will be returned to Applicant.

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-4 and 8-10, drawn to DNA encoding proteins and bacteria with enhanced protein activity, classified in class 435, subclass 252.33.

   II. Claims 5-7, drawn to methods for producing an amino acid, classified in class 435, subclass 106.

2. The inventions are distinct, each from the other because:

Groups I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the bacteria of Group I can be used to express a protein with an enhanced activity, the DNA of Group I can be used as a hybridization probe and the amino acid produced by the method of Group II can be chemically synthesized.

3. Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification(s), restriction for examination purposes is proper. "*For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP 808.02*" (see MPEP 803). The serious burden of search has been established by the different classification of the inventions, requiring divergent literature (patent and non-patent) and/or sequence searches.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

During a telephone conversation with Daniel J. Pereira on 04/25/01, a provisional election was made **with** traverse to prosecute the invention of Group I, claims 1-4 and 8-10. Affirmation of this election must be made by applicant in replying to this Office action. Claims 5-7 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Drawings

4. The four drawings submitted with this application have been approved for publication by a draftsperson.

Specification/Informalities

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed, for example "Novel Threonine Resistance Gene".

Claim Objections

6. Claims 1-4 and 8 are objected to because of the following informalities: the terms "threoine" in claim 1, "activity of protein" in claims 1-4, "in Sequence Listing" in claims 1 and 2, and "encode a protein" in claim 8 is misspelled and/or gramatically incorrect and should be replaced with, for example, "threonine", "activity of a protein" "of the Sequence Listing" and "encodes a protein", respectively. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1, 2, and 8-10 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is drawn to a bacterium (claims 1 and 2) or a DNA (claims 8-10). As written, the claims read on a product of nature and should be amended to

indicate the hand of the inventor, for example, by addition of the term "purified" or "isolated" to identify a product that is not found in nature. See MPEP § 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-4 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **The claims are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors**.

9. The term "enhanced" in claims 1-4 is unclear absent a statement defining to what the level of resistance or protein activity is being compared. The term "enhanced" is a relative term and the claim should define and clearly state as to what the resistance or protein activity is being compared (i.e., resistance or protein activity in comparison to what level of resistance or protein activity?).

10. Claims 1-4 are indefinite in the recitation of "activity of protein". The term "activity of protein" is not defined by the claim nor the specification and the meaning of this term is unclear. It is suggested that the term "activity of protein" be replaced with a term that clearly defines Applicant's intended protein activity.

11. The term "bacterium having the protein" in claims 1 (claim 3 dependent thereon) and claim 2 (claims 3 and 4 dependent thereon) is unclear and confusing. The term is not defined by

the claim nor the specification and the meaning of this term is unclear. It is suggested that the language be replaced with a term that has a more clearly identifiable meaning, for example, "bacterium expressing the protein".

12. The terms "in a cell of said bacterium" in claims 1 (claim 3 dependent thereon) and claim 2 (claims 3 and 4 dependent thereon) and "inversion" in claim 8(B) is unclear and confusing. The terms are not defined by the claim nor the specification and the meaning of this term is unclear. It is suggested that "in a cell of said bacterium" be replaced with a term that has a more clearly identifiable meaning, for example, "in said bacterium" and the term "inversion" be deleted.

13. Claim 9(b) is indefinite in the recitation of "a stringent condition" as the specification does not define what conditions constitute "stringent". What hybridization conditions are considered "stringent" varies widely in the art depending on the individual situation as well as the person making the determination. As such, it is unclear how homologous to the polynucleotide of nucleic acids 187 to 804 of SEQ ID NO:3 a sequence must be to be included within the scope of these claims. It is suggested that, for example, Applicants clearly identify a specific "stringent condition" within the claim.

14. Claim 9(b) is indefinite in the recitation of "a probe" as it is unclear from the specification as to what is encompassed by the term "a probe". It is suggested that, for example, Applicants clearly identify the intended meaning of the term "a probe" within the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-4 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of *Escherichia* bacteria expressing a polypeptide comprising SEQ ID NOs:4, SEQ ID NOs: 2 and 4, or deletion, substitution, insertion, or addition variants thereof (claims 1-4), or a DNA encoding the polypeptide of SEQ ID NO: 4 including substitution, deletion, insertion, or addition variants thereof (claim 8). The specification teaches only a single representative species of such bacteria, i.e., *Escherichia* bacteria expressing a polypeptide comprising SEQ ID NOs:4 or SEQ ID NOs: 2 and 4, and only a single representative species of such DNAs, i.e., the polynucleotide of SEQ ID NO:3. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being *Escherichia* bacteria with enhanced L-threonine resistance. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

16. Claims 1-4 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a bacterium expressing the polypeptide of SEQ ID NO:4, a bacterium expressing the polypeptides of SEQ ID NOs:2 and 4, or the polynucleotide of SEQ ID NO:3, does not reasonably provide enablement for a bacterium expressing a polypeptide comprising any deletion, substitution, insertion, or addition variants of SEQ ID NOs:4 or SEQ

ID NOs: 2 and 4, thereby conferring resistance to L-threonine and/or L-homoserine to said bacterium or a DNA encoding substitution, deletion, insertion, addition, or inversion variants of SEQ ID NO:4 and having an ability to confer resistance to L-threonine to a bacterium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1 (claim 3 dependent thereon), 2 (claims 3 and 4 dependent thereon) and 8 are so broad as to encompass a bacterium comprising any variants of SEQ ID NOs:4 or SEQ ID NOs: 2 and 4 that result in resistance to L-threonine and/or L-homoserine or any DNA encoding substitution, deletion, insertion, addition, or inversion variants of SEQ ID NO:4 resulting in an ability to confer resistance to L-threonine to a bacterium. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides and polynucleotides broadly encompassed by the claims. Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the polypeptide's structure relates to its function. However, in this case the disclosure is limited to a bacterium expressing the polypeptide of SEQ ID NO:4, a bacterium expressing the polypeptides of SEQ ID NOs:2 and 4, or the polynucleotide of SEQ ID NO:3.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a polynucleotide's sequence where nucleic acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any polynucleotide and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given polynucleotide to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a bacterium comprising any variants of SEQ ID NOs:4 or SEQ ID NOs: 2 and 4 that result in resistance to L-threonine and/or L-homoserine or any DNA encoding substitution, deletion, insertion, addition, or inversion variants of SEQ ID NO:4 resulting in an ability to confer resistance to L-threonine to a bacterium because the specification does not establish: (A) regions of the protein's structure which may be modified without effecting ThrR and/or RhtA activity; (B) the general tolerance of ThrR to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues of ThrR and/or RhtA with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a bacterium comprising any variants of SEQ ID NOs:4 or SEQ ID NOs: 2 and 4 that result in resistance to feedback inhibition by L-threonine and/or L-

homoserine or any DNA encoding substitution, deletion, insertion, addition, or inversion variants of SEQ ID NO:4, resulting in an ability to confer resistance to feedback inhibition by L-threonine to a bacterium. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Zakataeva et al. (IDS reference AY) Claims 1-4 and 8-10 are drawn to an *Escherichia* bacterium expressing a polypeptide comprising deletion, substitution, insertion, or addition variants of SEQ ID NOs:4 or SEQ ID NOs: 2 and 4, thereby conferring resistance to L-threonine and/or L-homoserine to said bacterium (claims 1-4) or a DNA encoding substitution, deletion, insertion, addition, or inversion variants of SEQ ID NO:4 and having an ability to confer resistance to L-threonine to a bacterium or a complementary DNA thereof.

Zakataeva et al. (AY) teach cloning of the novel *Escherichia coli* genes *rhtB* and *rhtC* (p 228, Introduction and Materials and Methods). Zakataeva et al. (AY) further teach the intercellular presence of homoserine lactone, homoserine, and threonine suppress the growth of *E. coli* (p 229, Results, paragraph 1) and that RhtB (product of the *rhtB* gene) carries out efflux of homoserine and homoserine lactone and RhtC (product of the *rhtC* gene) carries out efflux of threonine (p 228, Introduction). Zakataeva et al. (AY) disclose "Amplification of genes for components of systems that eliminate antibiotics, organic solvents, and metal ions from the cell increase the resistance of bacteria to these substances" (p 229, Results, paragraph 1) and that "In view of this, we found that cloning (using a multicopy vector) of an *E. coli* chromosomal DNA fragment from the 86 min region resulted in resistance of cells to homoserine lactone, homoserine, and threonine" (p 229, Results, paragraph 1). Zakataeva et al. (AY) also teach *E. coli* transformed with a plasmid with an *rhtB* gene insert (pNPZ42) conferred resistance to homoserine, *E. coli* transformed with a plasmid with an *rhtC* gene insert (pNPZ48) conferred resistance to threonine, and *E. coli* transformed with a plasmid with *rhtB* and *rhtC* genes (pNPZ41 or pNPZ46) conferred resistance to both homoserine and threonine (p 229, Fig 1 and Results, paragraph 2). This anticipates claims 1-4 and 8-10 as written.

Should Applicant present an argument that the reference of Zakataeva et al. (AY) cannot be applied in a rejection under 35 U.S.C. 102(a) due to the date of the publication, Applicant should provide an English translation of the priority document submitted with the instant application.

18. Claims 1-4 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Zakataeva et al. (IDS reference AZ). Claims 1-4 and 8 are drawn to an *Escherichia* bacterium expressing a

polypeptide comprising deletion, substitution, insertion, or addition variants of SEQ ID NOs:4 or SEQ ID NOs: 2 and 4, thereby conferring resistance to L-threonine and/or L-homoserine to said bacterium (claims 1-4) or a DNA encoding substitution, deletion, insertion, addition, or inversion variants of SEQ ID NO:4 and having an ability to confer resistance to L-threonine to a bacterium (claim 8). Zakataeva et al. teach two genes isolated from *Escherichia coli*, *rhtA* and *rhtB*, that when expressed in *E. coli* confer resistance to homoserine and threonine. Zakataeva et al. disclose "at least two genes, *rhtA* and *rhtB*, exist in *E. coli* that in multicopy confer resistance to these amino acids", i.e., threonine and homoserine. This anticipates claims 1-4 and 8 as written.

Conclusion

19. No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

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